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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/808,205	03/24/2004	Suzanne T. ILdstad	17541-040001	3925

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FISH & RICHARDSON P.C.
PO BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/808,205	ILDSTAD, SUZANNE T.	
	Examiner	Art Unit	
	Zachary Skelding	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment to the claims and remarks filed November 7, 2007 have been considered.

   Claims 1-27 have been canceled.

   Claim 28 has been amended.

   Claims 28-30 are pending.

   Claims 28-30 are under examination as they read on a method for conditioning a recipient for bone marrow transplantation comprising subjecting the recipient to total body irradiation and infusing the recipient with a donor cell preparation containing hematopoietic stem cells various days after total body irradiation.

2. This Office Action is a response to applicant's amendment to the claims and remarks filed November 7, 2007.

   The previous rejections of record can be found in the Office Action mailed June 7, 2007.

   The previous rejection under 35 U.S.C. § 112, 2nd paragraph has been overcome in view of applicant's amendment to the claims.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

   A person shall be entitled to a patent unless –

   (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 28-30 are rejected under 35 U.S.C. § 102(b) as anticipated by Sykes et al. (WO 02/40049)(see entire document).

   Applicant argues that Sykes does not teach that transplantation of bone marrow should be delayed following total body irradiation of a recipient. In particular, applicant argues Sykes, "is directed toward reducing GVHD associated with hematopoietic cell grafts by blocking molecules that allow donor T cells to migrate into host tissues. According to Sykes et al., one way to accomplish this is to separate BMT and donor T-cell infusion (page 7, lines 26-27). Sykes et al. also states that "[m]ethods of the invention avoid GVHD...by the use of conditioning regimens that are less toxic and less pro-inflammatory, followed by delayed administration of donor T- cells" (at page 7, lines 18-22)." Applicant concludes "Sykes is therefore not proposing to delay bone marrow transplantation," further pointing to Example 1

of Sykes on page 41 in support of this conclusion, "which describes bone marrow administration on the day following thymic irradiation."

First, given the teachings of Example 1 on page 41 of Sykes which "describes bone marrow administration on the day following thymic irradiation," as stated by applicant, the Examiner does not understand how this teaching could be understood as anything other than the claimed method, i.e., a method for transplanting a recipient with bone marrow comprising subjecting said recipient to a non-myeloablative dose of total body irradiation followed by infusing with donor bone marrow between 1 and 3 days following total body irradiation.

Also, while it is true that Sykes teaches delayed administration of donor T-cells following non-myeloablative irradiation, including an embodiment where BMT is separated from donor T-cell infusion, this is not the only teachings of Sykes concerning the delayed administration of donor cells following non-myeloablative irradiation as further described below.

In this regard, it is noted that "a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied,* 493 U.S. 975 (1989)." See MPEP § 2123.

Applicant further argues that (***emphasis added***), "Sykes et al. states that the 'greater susceptibility of lymphohematopoietic cells than other host tissues to destruction by MHC-specific donor T-cells is due to the immediate contact of donor cells with host cells...' (see page 7, lines 8-11). ***This passage, however, is with reference to T-cells. Accordingly, Sykes et al. proposes treatments to inhibit T cell activity prior to, during, and/or after administration of donor HSCs.*** According to Sykes et al., '***a pre-stem cell treatment...will be given to the subject about 1, 2, 3, 4, or 5 days prior to stem cell transplantation...*** [and/or]... a post-stem cell transplant treatment will be given about 1, 2, 3, 4, or 5 days after bone marrow transplantation' (***see page 12, lines 21-29***). ***These passages refer to administering a treatment to inhibit T cell activity*** 1 to 5 days before and/or after bone marrow transplantation ***and do not refer to delaying the bone marrow transplantation itself.***"

In contrast to applicant's argument, the Examiner's asserts that Sykes does refer to "delaying the bone marrow transplantation itself."

To best understand the meaning of the passage that applicant quotes from page 12, lines 21-29 of Sykes it helpful to consider it in the context in which is appears, starting from page 10, 2nd paragraph of Sykes and continuing through page 12, 4th paragraph (as shown below, ***emphasis added***):

"In general, the invention features, in a first aspect, a method of treating a subject e. g., a human, having a hematologic disorder, e. g., a hematologic malignant disorder, e. g.,

leukemia. The method includes ***administering donor hematopoietic stem cells under conditions which minimize GVDH and maximize GVL, thereby treating the disorder, e. g., relieving or alleviating one or more symptoms of the disorder.***

In methods described herein, the donor is from the same species as the subject, or from a different species. In allogeneic methods the donor of stem cells and the donor of leukocytes should be the same individuals. In xenogeneic methods, the subject is a mammal, preferably a primate and more preferably a human. The donor mammal is, by way of example, a swine, e. g., a miniature swine, or a nonhuman primate. In xenogeneic methods the donor of stem cells and the donor of leukocytes need not be the same individual but is from a different individual which is MHC matched or highly inbred, e. g., inbred miniature swine which are MHC matched.

While not wishing to be bound by theory, the myeloreductive non-myeloablative treatment is believed to prepare the subject for the induction of mixed chimerism and has a cytoreductive effect on cancer cells. ***The myeloreductive non-myeloablative treatment should be administered prior to introduction of the donor hematopoietic stem cells, preferably sufficiently prior to the administration of donor hematopoietic stem cells such that if it includes the administration of a chemical agent, the chemical agent will be cleared from the circulatory system prior to the administration of donor hematopoietic stem cells.***

Preferred myeloreductive non-myeloablative agents are alkylating agents, e. g., cyclophosphamide, or fludarabine or similar substances, however, hematopoietic space creating antibodies or drugs, e. g., inhibitors of cell proliferation, e. g., DSG, or an anti-metabolite, e. g. brequinar, or an anti-T cell antibody, e. g., one or both of an anti-CD4 or anti-CD8 antibody is used as a myeloreductive non-myeloablative agent.

In preferred embodiments, the myeloreductive non-myeloablative treatment is sufficiently mild that at lest 10, and more preferably at least 30, 50, or 75% of the subjects to which it is administered will form mixed chimeras (as opposed to having their bone marrow totally ablated).

In preferred embodiments, immune cell activity, e. g., T cell activity, preferably graft reactive T cell activity, is inhibited in the subject. While not wishing to be bound by theory, the inhibition of T cells is believed to prepare the subject for the induction of mixed chimerism by inhibition of subject T cell activity which would mount an immune response against the donor hematopoietic stem cells and to inhibit donor T cell activity which would mount an immune response against the subject (GVHD).

Numerous methods of inhibiting T cell activity are suitable for use in methods described herein. By way of example, these include: the administration of anti-T cell antibodies, e. g., an ATG preparation, polyclonal or monoclonal antibody directed against CD4, CD8, or CD2 (an anti-CD2 antibody, e. g., the anti-CD2 monoclonal antibody BTI-322 or a humanized version thereof, or an antibody which overlaps or binds the epitope recognized by BTI-322, are particularly useful); the administration of an agent, e. g., an antibody, which blocks or

otherwise inhibits a pathway, e. g., a costimulatory pathway, of T cell activation (agents, e. g., antibodies, which block the CD28-B7 pathway, e. g., a CTLA4-IgG fusion protein, or agents, e. g., an antibody which blocks the CD40-gp39 pathway, e. g., an anti-gp39 antibody, are particularly suited for use in the method), or generally, by the administration of a treatment which down modulates or otherwise inhibits one or more of the T cell receptor, CD4 co-receptor, CD8 co-receptor or other receptor or co-receptor which promotes T cell activation or maturation; the administration of an immunosuppressive agent, e. g., cyclosporine, FK506, or rapamycin; ***and the administration of thymic irradiation, or other treatment which creates thymic space.***

Treatments which inhibit T cell activity are administered at any time in the course of the method but should not be such that donor T cells will be entirely eliminated. ***Treatments are administered prior to, at the same time as, or after, the administration of donor hematopoietic stem cells.*** Preferably, such treatments are provided both before and after the administration of donor hematopoietic stem cells. ***Treatment prior to the administration of donor hematopoietic stem cells is believed desirable in that it will condition the subject for the receipt of the donor hematopoietic stem cells.*** Treatment after the administration of donor hematopoietic stem cells is believed desirable in that it will reduce donor-immune attack on the host and further promote acceptance by the subject of the donor hematopoietic stem cells.

For best results, treatments to inhibit T cell activity, e. g., anti-T cell antibodies or cyclosporine, are administered repeatedly. e. g., ***such treatment is administered one, two, three, or more times prior to donor bone marrow transplantation. Typically, a pre-stem cell treatment, e. g., the administration of antibodies, will be given to the subject about 1,2,3,4, or 5 days prior to stem cell transplantation.*** It is desirable to repeat pre-stem cell administrations every 1-5 days until the subject shows excess antibodies in the serum and about 80, 90, or 99% depletion of peripheral T cells and then to perform the stem cell transplantation. Treatments are also administered one, two, three, or more times after donor hematopoietic stem cell transplantation. Typically, a post-stem cell transplant treatment will be given about 1,2,3,4, or 5 days after bone marrow transplantation.

Given the highlighted teachings of Sykes quoted above, including that "***[n]umerous methods of inhibiting T cell activity*** are suitable for use in methods described herein," such as "the administration of thymic irradiation," and that "***[t]reatments which inhibit T cell activity***... are administered prior to, at the same time as, or after, the administration of donor hematopoietic stem cells," it is unclear how the passage quoted above does not encompass in its breadth, for example, inhibiting T cell activity via myeloreductive non-myeloablative total body irradiation, followed 1, 2, 3, 4, or 5 days thereafter by donor bone marrow administration.

In conclusion, applicant has not convincingly argued that Sykes fails to anticipate the instant claims.

It should be noted that Sykes uses the phrases ""hematopoietic stem cells" and "stem cells" interchangeably throughout the publication. Moreover, Sykes defines "hematopoietic stem cells", as, for example, bone marrow cells capable of developing into all myeloid and lymphoid lineages and by virtue of being able to self-renew provides long term hematopoietic reconstitution (see Sykes, page 23, 3rd paragraph). In this same section (page 23, 3rd paragraph), Sykes further teaches that "[p]urified preparations of hematopoietic cells or preparations, such as bone marrow, which include other cell types, are used in methods of the invention."

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claim 28 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 5,514,364 (cited herewith); claim 2 of U.S. Patent No. 5,635,156 (cited on applicant's IDS of October 29, 2004), and claim 2 of U.S. Patent No. 5,876,692 (cited on applicant's IDS of October 29, 2004). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claim is anticipated by the claims of the reference claims, essentially for the reasons of record as put forth in the Office Action mailed June 7, 2007.

Applicant requests that this rejection be held in abeyance until allowable subject matter is indicated.

Applicant's request is acknowledged, however, Applicant is advised that the instant rejection will be maintained until such time as a terminal disclaimer signed by the assignee and fully

compliant with 37 CFR 3.73(b) is submitted.

7. Claims 28 and 29 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 5,635,156 and claim 2 of U.S. Patent No. 5,876,692, each in view of Sykes et al. (WO 02/40049), essentially for the reasons of record as put forth in the Office Action mailed June 7, 2007.

   Applicant requests that this rejection be held in abeyance until allowable subject matter is indicated.

   Applicant's request is acknowledged, however, Applicant is advised that the instant rejection will be maintained until such time as a terminal disclaimer signed by the assignee and fully compliant with 37 CFR 3.73(b) is submitted.

8. Claim 28 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over copending:

   Claims 18-20 of USSN 10/702,058;
   Claims 11-13, 23 and 26 of USSN 10/134,016;
   Claims 7, 11-13 of USSN 10/558,513; and
   Claim 2 of USSN 10/558,516,

   essentially for the reasons of record as put forth in the Office Action mailed June 7, 2007.

   Applicant requests that this rejection be held in abeyance until allowable subject matter is indicated.

   Applicant's request is acknowledged, however, Applicant is advised that the instant rejection will be maintained until such time as a terminal disclaimer signed by the assignee and fully compliant with 37 CFR 3.73(b) is submitted.

9. Claims 28 and 29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable as being unpatentable over copending:

   Claims 18-20 of USSN 10/702,058;
   Claims 11-13, 23 and 26 of USSN 10/134,016;
   Claims 7, 11-13 of USSN 10/558,513; and
   Claim 2 of USSN 10/558,516,

   each in view of Sykes et al. (WO 02/40049),

   essentially for the reasons of record as put forth in the Office Action mailed June 7, 2007.

Applicant requests that this rejection be held in abeyance until allowable subject matter is indicated.

Applicant's request is acknowledged, however, Applicant is advised that the instant rejection will be maintained until such time as a terminal disclaimer signed by the assignee and fully compliant with 37 CFR 3.73(b) is submitted.

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding, Ph.D.
Patent Examiner
January 17, 2008

MICHAIL BELYAVSKYI, PH.D.
PRIMARY EXAMINER

1/17/08